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The Actions of Atropine and Quinidine in Fibrillation of the Auricles; Clinical and Experimental Studies

Second Lecture

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THE ACTIONS OF ATROPINE AND QUINIDINE IN FIBRILLATION OF THE AURICLES; CLINICAL AND EXPERIMENTAL STUDIES.

SECOND LECTURE*

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UNIVERSITY COLLEGE HOSPITAL, LONDON, ENGLAND.

In studying the action of quinidine upon the fibrillating auricle and in considering the nature of this action, we may conveniently begin by noticing certain effects of vagal stimulation, and certain effects of abolishing vagal tone, upon the mammalian auricle.

For many years it has been customary to regard an increased vagal tone as having a purely depressant effect upon the functions of the mammalian heart muscle. We know that vagal stimulation slows the natural heart beat, produces heart-block at the *A-V* ring, that it notably reduces the force of the auricular contractions and that, under vagal stimulation, the auricle will no longer respond to electric shocks of previously threshold strength. From these observations it has been natural to conclude that the vagus tends to inhibit rhythmic impulse formation in the heart, that it hinders conduction in the heart, and that it reduces the force of the muscular contractions and decreases the excitability of the muscle. We have been tempted to apply all these conclusions to the muscle of the heart generally, and especially to the auricle, in considering the action of the vagus upon forms of auricular disorder. If we are to avoid serious fallacy, we must particularize and avoid transferring a conclusion which applies to one section of heart muscle to a second section. Since vagal stimulation reduces the power of the *A-V* tissues to conduct in the mammalian heart,

* Observations carried out on behalf of the British Medical Research Council at University College Hospital Medical School (London). A Wiley-Noble-Jones Lecture, delivered at the University of Oregon Medical School, Portland, in May, 1922. In this lecture I have utilized much material, as yet unpublished in detail and collected in collaboration with my coworkers, Dr. A. N. Drury, Dr. C. C. Iliescu and Dr. A. M. Wedd.

The third and last lecture will appear in the August issue of this publication; the first lecture appeared in the June issue.

there would seemingly be little risk in concluding that its action is similar upon the muscle of the auricle itself, for this muscle is known to be powerfully controlled by the inhibitory nerve. But the risk of such conclusions is a grave one, as this example illustrates; recent observation has shown quite clearly that the vagus has not the power to depress auricular conduction. If the mammalian auricle is beating normally, vagal stimulation leaves conduction in this muscle unchanged. Furthermore, if for any reason the rate of conduction is primarily reduced in the auricle, then vagal stimulation exerts a paradoxical effect; it increases the rate of conduction. For the purposes of this lecture we are concerned chiefly with depressed conduction due to an increased rate of beating, such as occurs in flutter and in fibrillation; in the case of conduction slowed by this cause, vagal stimulation brings transmission rates back to normal.[8] The meaning of this becomes clearer if we recognize that this disturbed conduction is connected with the refractory period of the muscle under observation. If a new stimulus falls on the muscle before it has obtained sufficient rest, it finds this muscle only partially recovered; it is partially refractory, and the wave propagated therefore travels slowly. When the vagus is stimulated, the contraction of the muscle is much reduced in amplitude, it is also conspicuously reduced in its duration;[8] the systoles are now very brief and the rest periods between the responses become sufficiently prolonged to permit complete recovery.

Thus, from recent observation come two conclusions: Vagal stimulation (1) conspicuously reduces the length of the refractory period and (2) it quickens conduction in an auricle which is beating rapidly. Section of the vagi, or atropinization, [8 11] have the opposite effects. These two conclusions are of much consequence when we consider the effects of vagal stimulation upon the fluttering or fibrillating auricle.

Our reasons for the belief that auricular flutter and fibrillation are dependent upon a circus movement have been discussed at some length,* and for the purposes of this lecture I ask you to accept this conclusion. The maintenance of a circus movement in the auricle depends on certain factors which we may now examine in some detail.

It is essential that as the wave circulates, a gap between its crest and wake should be maintained. Otherwise the crest of the wave, in advancing, will find no responsive muscle ahead of its movement. Upon the existence of this gap, the maintenance of the movement depends absolutely.

The Length of Gap. Start a wave in one direction along a circular path. The wave begins at one point, and moves around the circle.

* The nature of flutter and fibrillation was the theme in two preliminary lectures of this series, the ground covered being very similar to that covered by the Oliver-Sharpey lectures[6] of 1921.

The muscle at the starting point becomes refractory or unresponsive as it receives the wave; it remains unresponsive for a given length of time, a period termed the *refractory period.*

The shorter this refractory period, the smaller will be the distance which the wave travels before the starting point again enters the responsive state. The shorter the distance travelled by the wave in a given time, the greater will be the gap left between its crest and the starting point to which it is returning. The distance travelled will be less, the slower the wave moves; a longer gap results therefore from slower conduction. Finally, the longer the path to be travelled by the wave, the longer will be the gap. Thus, the length of gap is determined by three factors:

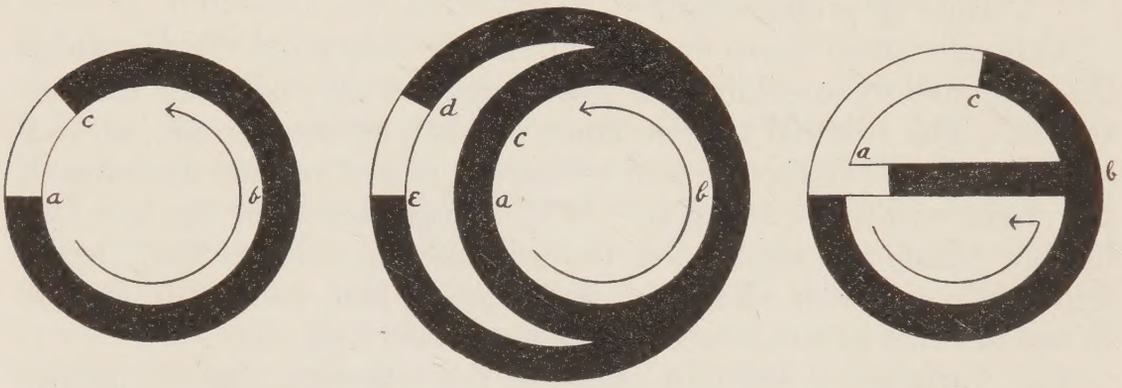
1. Length of path.
2. Duration of refractory period.
3. Rate of propagation.

Although these three factors obviously *determine* the length of the gap, strictly speaking it is not correct to say that they all control it. The original muscle tract persists unaltered and, so long as the state of conduction and refractory period remain unchanged, the wave will move along it. It is change in one of the last two factors, which can alone alter the original gap. Refractory period and conduction rate alone *control* the gap. But, subject to change in one or other of these factors, the path itself may vary.

This variation is brought about in the following way. Suppose that the refractory period lengthens or the rate of propagation increases, the gap shortens. If from either of these causes the gap *disappears,* the wave does not necessarily cease to circulate; it will continue to circulate if a longer channel is open to it (Fig. 1 *b*). Reversely, if the refractory period shortens, or the rate of propagation decreases, the gap will widen and, in widening, it may open up to the wave a shorter channel, which the wave will then pursue (Fig. 1 *c*). The moment lengthening or shortening of the path occurs, this change will also affect the length of gap; but it is to be emphasized that this change is secondary to change in the remaining factors and consequently becomes of secondary importance theoretically, when changes in the gap are considered. These remarks bring me to discuss our problem in a different manner.

The Number of Circuits per Minute. As the wave is continuous, the number of circuits per minute depends solely upon the circulation time. It will be at once evident that the time of circulation is determined by the length of the path and the rate at which the wave travels; refractory period exerts no direct influence. The circulation time will be shorter, and the circuit movements will be more numerous if the path is short and the rate of propagation rapid; conversely, the time will be longer, and the circuit movements fewer, if the path is long and the rate of propagation slow. But refractory period cannot be left out of the account, it is sub-

ject to variation; by increasing it can force the wave to travel upon a longer channel, by decreasing it can induce the wave to flow upon a shorter channel. Variations in the length of the path are controlled by the dominant factors, refractory period and rate of conduction. It is to these two that we constantly return, from whichever standpoint we regard the wave. The length of path becomes a secondary consideration. A shorter circulation time, an increase in the number of circuit movements per minute is induced: (*a*) By an increased rate of conduction and (*b*) by a decrease in the refractory period when this permits the wave to accept a shorter path. Conversely a decrease in the number of circuit movements per minute is induced: (*c*) By a decreased rate of conduction and (*d*) by an increase in the refractory period when this forces the wave into a longer channel.



A. B. C.

FIG. 1. A.—A diagram of a wave circulating in a ring of muscle. The wave travels in the direction *a*, *b*, *c*. *c* represents the crest of the wave and *a* represents its wake; these travel at the same rate and leave between them a constant gap of responsive muscle *ca*. The muscle which is refractory, *i. e.* in a state of contraction, is represented black. Suppose now that the refractory period suddenly lengthens; the muscle at *a* will remain refractory for a longer time and, as the crest *c* is all the time advancing, the gap *c a* will tend to close. If it closes, the circus movement on the original path (*abc*) will be brought to an end (Fig. 1 B); but the circus movement may itself continue if a new and longer channel (*d e*) is open to it (Fig. 1 B). Similarly if, while the conditions are those of Fig. 1 A and the refractory period suddenly shortens, the gap will increase in size. This increase in the length of the gap may open up a new channel (*b a* in Fig. 1 C) upon which the wave is now able to circulate.

These are the broad effects, though the question is a complex one. An increase or decrease in the rate of conduction will be mainly, perhaps solely, effective when the original gap is a material one. An increase or decrease in the refractory period will be mainly or solely effective, when the original gap is small and the wave is free, at the change, to take a shorter or longer channel.

The path may also change, theoretically, as a result of change in the rate of conduction. If this occurs, the effect of the secondary change would tend to neutralize the effect of the primary change, so far as an influence on rate of circulation is concerned. It is even conceivable that a decreased rate of conduction might lead, by materially shortening the path, to a decrease in circulation time

(or an increase of the first to an increase of the second); but these paradoxical effects could only occur in very special circumstances. It is here to be remarked that probably in auricular muscle beating at a high rate, change in conduction and in the refractory period never occur apart from one another. Slow conduction appears always to be associated with lengthened refractory period;

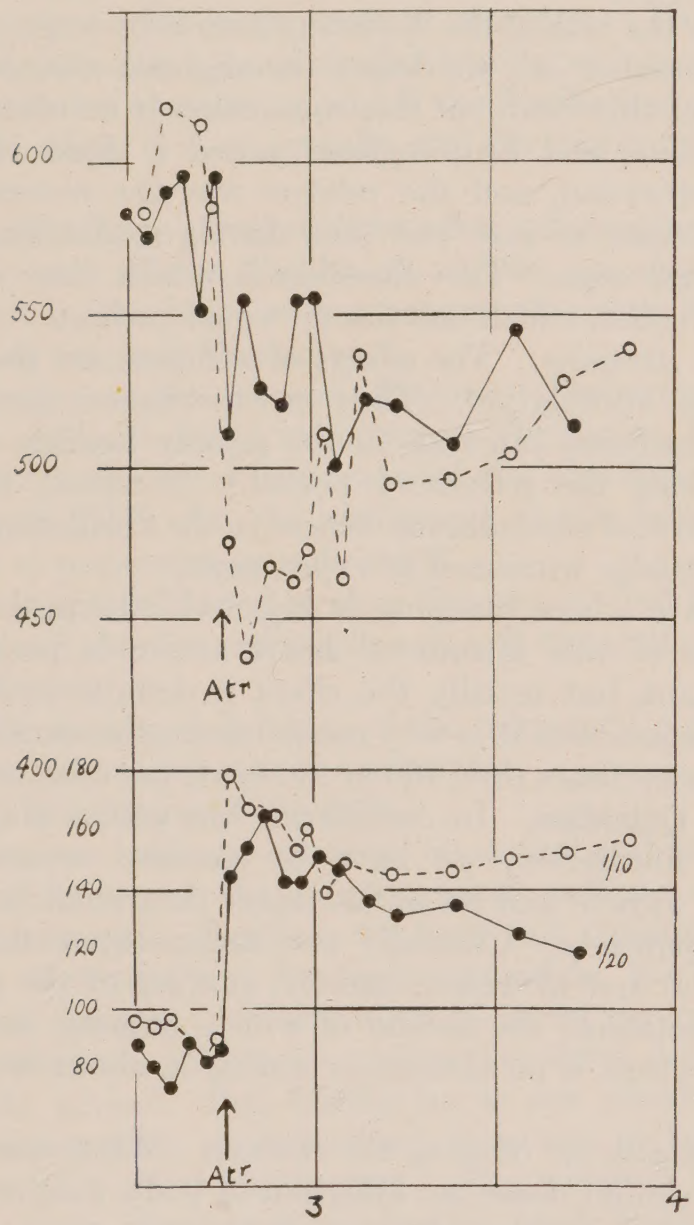


FIG. 2.—A chart from a case of fibrillation of the auricles, showing the effect of injecting $\frac{1}{20}$ and $\frac{1}{10}$ of a grain of atropine intravenously. The ventricular rate (lower curves) rises; the auricular rate (upper curves) falls. In these instances the falls of auricular rate are unusually conspicuous. Note that the reaction to $\frac{1}{10}$ is greater than to $\frac{1}{20}$ of a grain of atropine.

at all events this is so far as the variations described in the present lecture are concerned. These two changes, acting in concert, but in opposite directions so far as they influence the length of path, tend to neutralize each other.

The Action of the Vagus. Consider the action of the vagus, in the light of this theory of circuit movement: by reducing the trans-

mission time it will expedite the circus movements; if, by reducing the refractory period, it reduces the length of path, the reaction will be in the same direction. Thus, vagal stimulation should accelerate the movements of the auricle in flutter and in fibrillation. It is well known to do so in experiment.[9] [12] Clinically it is difficult to obtain a sufficiently powerful stimulation and, as a rule, little change of auricular rate is to be observed; thus, in recent attempts to alter the rate of the fluttering auricle by vagus pressure we have failed, neither can we detect the slightest change of rate in past records of this kind; in this connection it is interesting to observe that Levine and Frothingham[5] noted a slight change of rate in deep respiration, and the *relation* was the reverse of the normal; the increase of rate was seen during expiration, an act which exalts vagal tone. The direction in which they observed change is the direction which our theory would predict.

The Action of Atropine. The effects of atropine are the reverse of those of vagal stimulation. Thus in experiment, atropine increases the transmission intervals in the rapidly beating auricle;[11] it tends to prolong the refractory period.[8] Atropine, therefore, should slow the rate of auricular movement in the fibrillating auricle. This effect is actually witnessed in experiment.

The fall of rate where atropine is injected into patients who are the subjects of this disordered heart action is perhaps not absolutely constant, but usually the effect is definite and may be conspicuous, in some cases it is very conspicuous, the auricular rate falling often 50, sometimes even 100 or 150 beats per minute (Fig. 2).

The Action of Quinidine. In considering the action of quinidine upon auricular fibrillation, we have to consider separately its action upon the auricle and its action upon the ventricle. These will be taken separately. Clinically two actions upon the auricle are witnessed, the first of which, namely, slowing of the auricular movements, is constant; the second of which, namely, restoration of the normal rhythm, is inconstant, occurring in about 50 per cent of our cases.

Action of Quinidine in Slowing the Auricle. When quinidine is given to dogs in similar doses per kilogram of body weight to those used therapeutically, among other reactions two stand out from our present point of view. Quinidine conspicuously lengthens the refractory period of the auricle; it lengthens this period 50 to 100 per cent. Its action in this respect is the most powerful known to be produced by therapeutic doses of any drug now used in cardiac maladies. The drug has a further action: it slows conduction in the auricular wall; the transmission intervals widen out; the increase is variable, but is usually from 50 to 100 per cent.[11]

Lengthened transmission intervals, according to the theory of circus movement, would profoundly slow the auricular rate. The longer refractory period of the muscle, if it exerted an influence

upon rate, would act in the same direction; for if sufficiently prolonged it would divert the wave upon a longer path. Reflection will show that an equal percentage increase in refractory period and conduction time, would leave the wave in the same path, would leave the gap unaltered, but would double the time of its circulation and halve the number of circuits completed. Only when the effect on the refractory period outweighed that on conduction, would the path tend to lengthen. Thus, knowing the effects of quinidine upon auricular muscle, we are able to anticipate its influence on the rate at which the fibrillating auricle beats. It should produce, it does actually and invariably produce, profound slowing.

Thus, the effects of vagal stimulation, of atropine and of quinidine upon the rate of the fibrillating auricle, are clearly explained, if we accept as the basis of our argument, circus movement as the underlying cause of fibrillation.

Restoration of the Normal Rhythm. Theoretically, the normal rhythm can be restored in flutter or fibrillation, by closure of the gap between the crest and wake of the circulating wave, and by this means only; for the movement should continue so long as this gap of responsive muscle exists.

What factors will tend to close this gap so that it cannot reopen? The gap will shorten and tend to close if one of the following events happen alone:

1. An increased duration of the refractory period.
2. An increased rate of conduction.
3. A shortening of the path.

The last we need not consider, for actual and final closure would not occur so long as the longer original path remained open as an optional channel. Further, we need not consider an increase in the rate of conduction, for under quinidine, the reverse happens. Closure of the gap and the ending of circus movement would however receive an adequate explanation from lengthening of the refractory period. But fibrillation is not always terminated by the administration of quinidine; it is not to be expected, since quinidine also slows conduction. The widened refractory period tends to close, the slowed conduction tends to open the gap; and it is only when the first effect exceeds the last that closure is to be anticipated. There is another reason why fibrillation should not always terminate under quinidine. Closure of the original gap may divert the circus movement along a longer path. A further increase in the refractory period might then prove effective, or it might not; the end result would depend on the extent of the longest available path.

It is evident that, knowing the effects of quinidine upon the muscle, and applying this knowledge to the theory of circus movement, we might anticipate the actual end results which are wit-

nessed. Abrupt termination of the disorder in one case, failure to terminate in another.

Before leaving these effects of quinidine upon the auricular disorder, it is to be noted that quinidine does not act on the muscle alone; it also acts on the vagus. Its effect is to paralyze this nerve partly or completely. The manner of its action is not the same as that of atropine, for atropine acts on the nerve endings, while quinidine would appear to act, according to Dale's recent observations,[1] upon the nerve ganglia; the end result, so far as we are now concerned, is the same. Vagal tone decreases. Fortunately for our theoretical consideration, this change in nerve control acts in the same directions as do the direct effects on the muscle, a fact which is expressed correspondingly in the accompanying table.

TABLE.

	Refractory period.	Transmission time.	Rate of auricular movement.
Vagal stimulation	−	−	+
Atropine	+	+	−
Quinidine (direct action)	+	+	
Quinidine (indirect action)	+	+	−

Since both the direct and indirect action of quinidine are similar in end-results to those of atropine, it may be asked why the last drug is not capable of bringing fibrillation to an end. The reply is that in some circumstances it does do so; for the fibrillating auricle of the dog, atropine is usually an effective remedy,[7] [14] stopping the disorder immediately. It is clear however that it is not effective clinically in chronic cases of fibrillation; though it might be so in more acute cases. A statement has been made that Hering[3] saw fibrillation abolished by atropine in man. This does not appear to have been so, the case being a disorderly rhythm of a different kind, as Hering[4] has stated. In patients, fibrillation is more firmly rooted than in dogs in which it has been produced by stimulation; and atropine, though it acts in the same directions as quinidine, has a far less powerful action.

It may be of interest to note that our observations upon atropine preceded our personal acquaintanceship with quinidine and its use in fibrillation.

The effect of Quinidine on the ventricles in fibrillation of the auricles is a complex one. In chronic fibrillation, a rise of ventricular rate is almost constant and is usually conspicuous. The rise coincides with the fall of auricular rate when single doses of the drug are given; using repeated doses, the ventricular rate often tends to fall away, although the auricular rate still remains low. Three factors appear to be involved, namely, the fall of auricular rate, loss of vagal tone and a direct action of quinidine on the conducting tissues. We may consider these separately.

When the auricle is beating rapidly and the ventricle is failing

to respond to all the impulses so created, a fall of auricular rate tends to raise the rate of the ventricle. That is so because, as is well known, the degree of block becomes less as the auricular rate falls. In treating patients with quinidine this reaction is sometimes shown, unequivocally; thus sometimes, if the auricular rate is driven down to the neighborhood of 200 beats per minute, the ventricle, which previously responded to each second beat of the auricle, suddenly assumes the full auricular rate; there is an abrupt rise of ventricular rate to approximately double its former level. Such an abrupt rise can have but one meaning, it is a pure response to the events in the auricle. When, however, we deal with the more gradual rise in the earlier stages of administration, it is less easy to estimate accurately the part played by auricular rate, though we may be sure that this influence is exerted. Its degree is difficult to estimate because we must presume that vagal tone may also be changing.

To what extent are the vagi paralyzed by quinidine, given in therapeutic doses? If the action is comparable to that witnessed in experiment the paralysis should be considerable. Yet it can be shown that this is not the case, for if a single dose of quinidine is given, amounting to 0.6 or 0.8 gm., then an injection of atropine at the height of the quinidine reaction lifts the ventricular rate very appreciably (Fig. 3). Moreover, the rate, to which the ventricle can be forced by atropine alone, is a good deal higher than that which is attained under quinidine (Fig. 4), except in those cases in which the auricular rate falls so low that the ventricle attains the full auricular rate. The vagal paralysis produced clinically is at the most only partial. But the *number of beats* by which the ventricular rate rises, is greater when atropine is given alone than when atropine is given to a patient in whom the ventricular rate is already raised by quinidine (Fig. 4). This indicates that paresis of the vagus does play a part, though the degree in which this factor participates appears to be variable. An action upon the vagi as powerful as that seen in experiment is improbable, since in the case of dogs the alkaloid is given intravenously and in man it is given by the mouth.

In experiments upon animals, almost all workers have noted that quinidine depresses conduction at the *A-V* junction. [2 11 13] This is more notable if the auricular rate is artificially maintained at a high level. It is due to a direct action on the muscle, for atropine or vagal section does not affect it. Such an effect, if it exists in man, must influence the ventricle in the reverse direction to that so far discussed. Now this effect does exist in man, for in most instances where there is a sudden resumption of the normal rhythm the *P-R* interval is seen to be prolonged (Fig. 5); and this prolongation is clearly due to quinidine, for it disappears during the following twenty-four hours, if the administration of the

drug is brought to an end. To what extent this controlling action upon the ventricle is exerted during the treatment of patients with

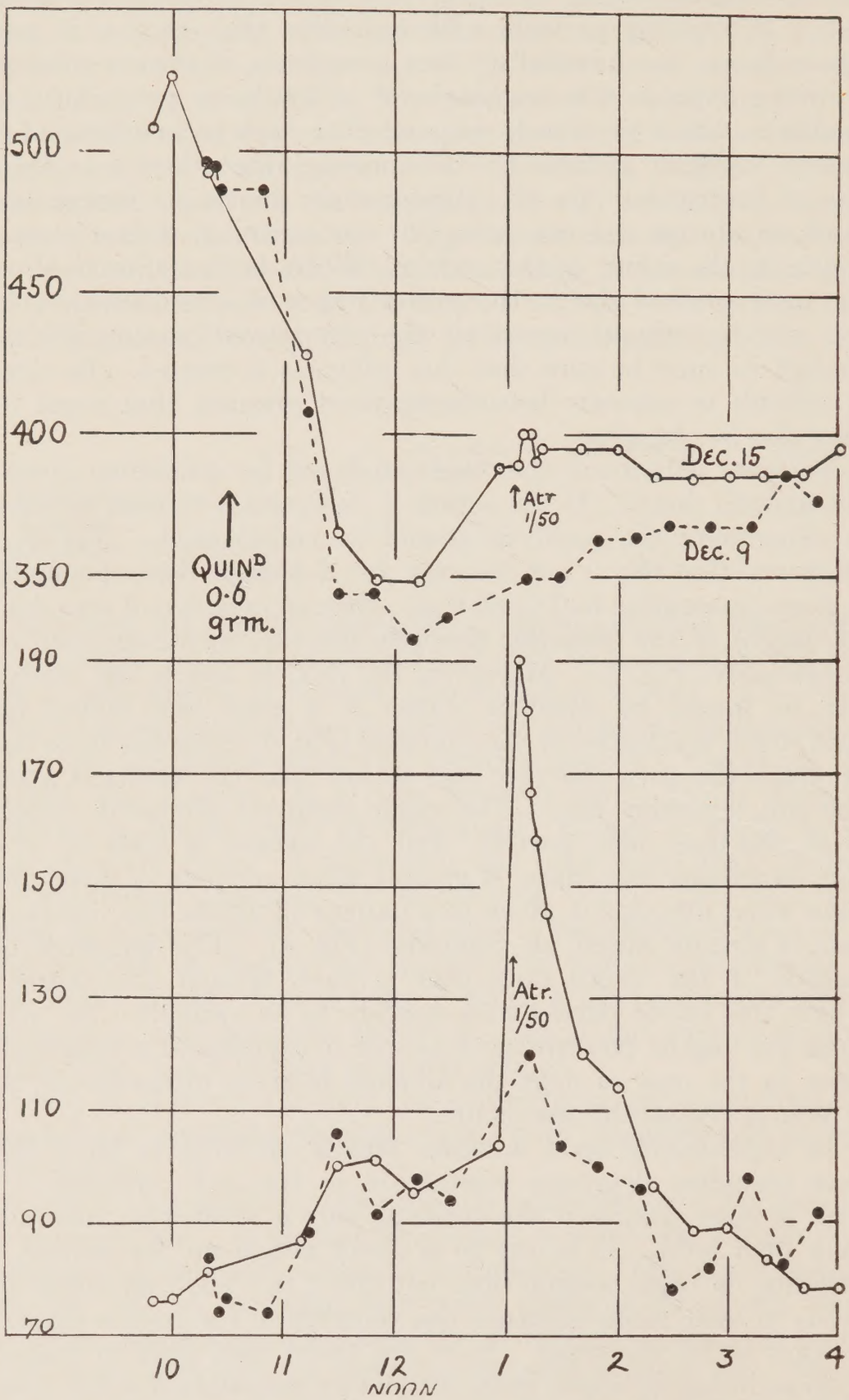


FIG. 3.—A chart from a case of auricular fibrillation, comparing the effect of a single dose of 0.6 gram of quinidine (black circles) with a similar dose of quinidine to which an intravenous dose of atropine has been added (plain circles). To show that the vagi are not paralyzed by the quinidine.

quinidine it is not as yet possible to say; many more observations are required before this question can be regarded as settled. The

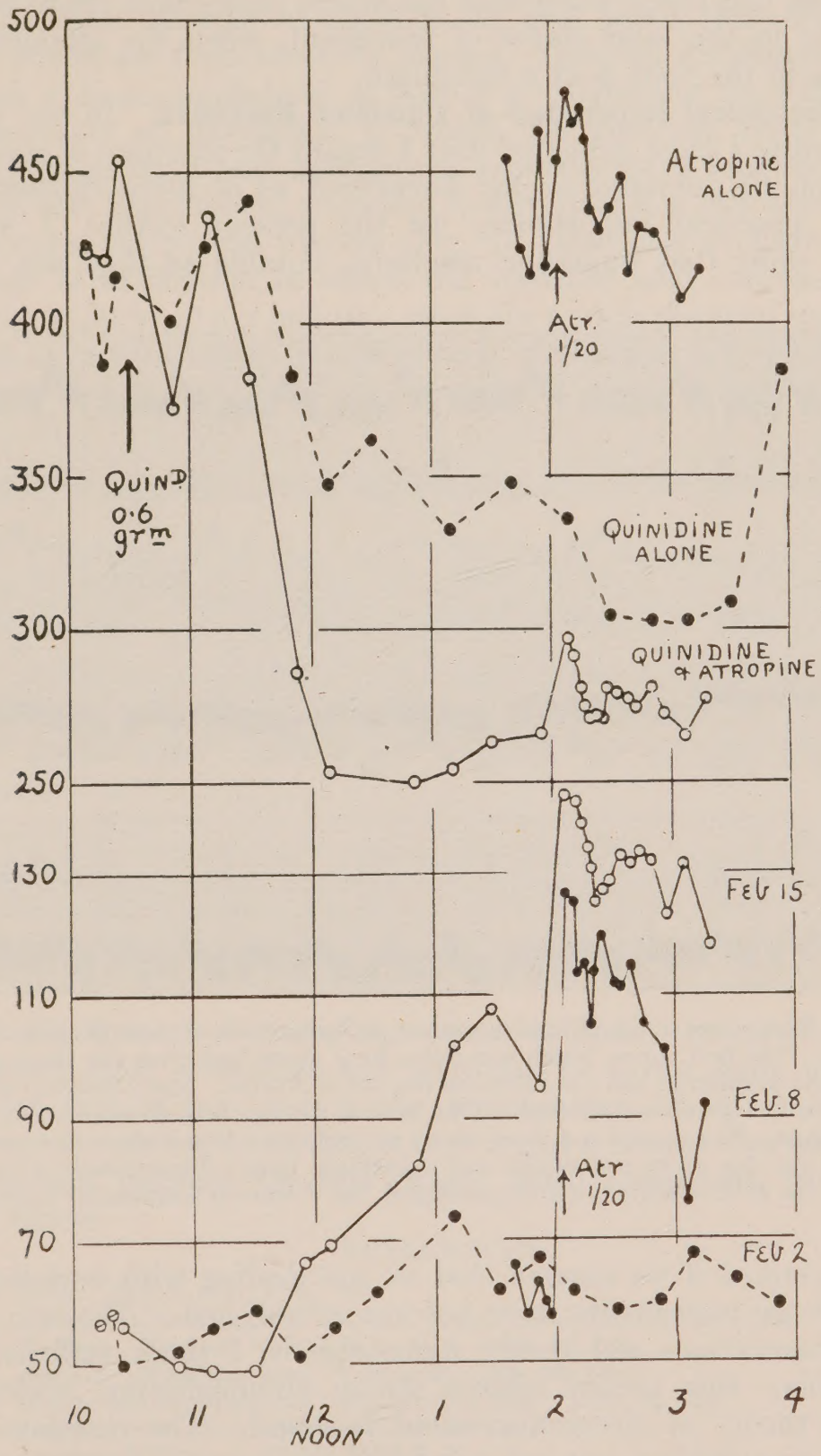


FIG. 4.—A chart from a case of auricular fibrillation, comparing the effect of (a) a single dose (0.6 gram) of quinidine (black circles, and broken line), of (b) a similar dose of quinidine to which an intravenous injection of atropine has been added (plain circles) and of (c) an injection of atropine alone) black circles and unbroken line).

only indication of its influence during the administration of the alkaloid and while the auricles are still fibrillating is found in the

tendency in many cases for the ventricular rate to fall when treatment is prolonged, a tendency otherwise unexplained. It would seem from this observation that the action comes into appreciable play only in the later stages of treatment, when the amount of quinidine in the body is at a maximum.

The Theoretical Importance of Quinidine Reactions. In my previous lecture I have indicated that I regard the reactions of clinical fibrillation to quinidine so far discovered as of more theoretical than of practical importance. In the present lecture, I have tried to show that quinidine reactions, notable as they are, are

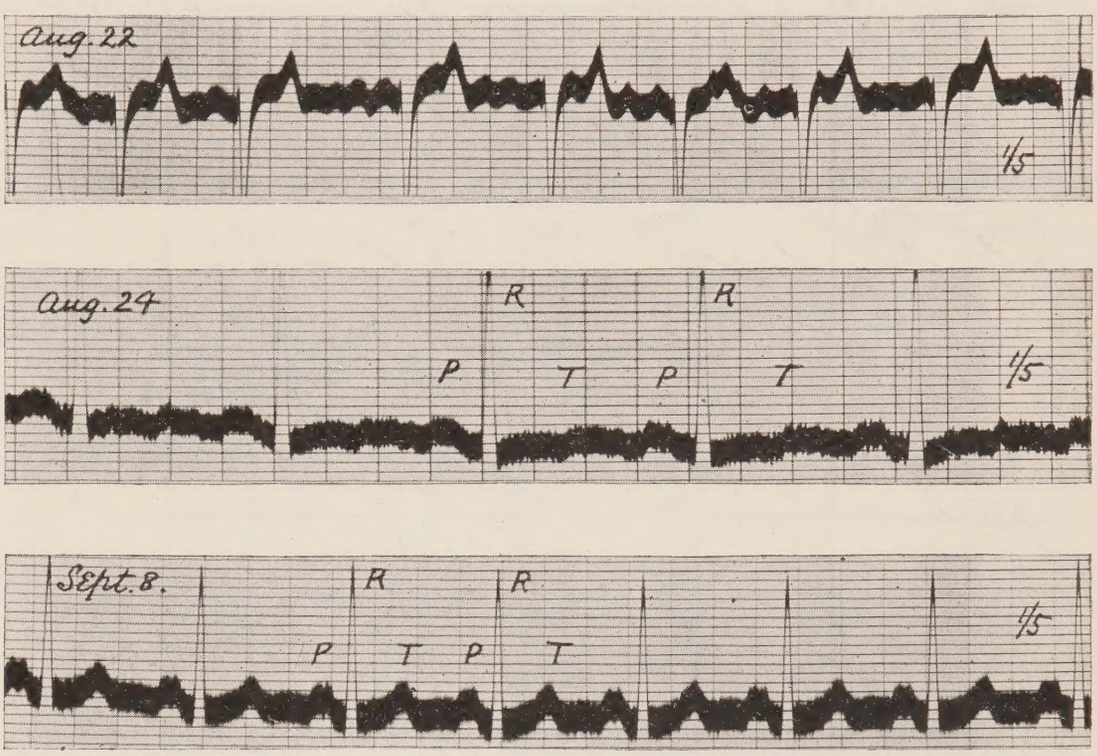


FIG. 5.—Three curves taken from a patient suffering from chronic fibrillation of the auricle. The first curve, which was taken by a direct lead from the chest wall, illustrates the fibrillation and was taken on the 22d of August. Quinidine was given amounting to 2.4 grams in two days. The normal rhythm became restored on the 24th of August. The second and third curves are from lead II and show this normal rhythm on the day of its restoration and a fortnight later. Immediately after its restoration the *P–R* interval is a little prolonged; the *T* wave is temporarily inverted.

to be explained if we assume that we are dealing with auricles in which circus movements have become established. The way in which observations and theory harmonize is, I think, sufficiently remarkable; this accord affords strong circumstantial evidence that the theory of circus movement is sound. The reactions of the heart to quinidine test a theory which, if true, is of fundamental consequence to our conceptions of disordered rhythm. They are severe tests; nevertheless, the theory still holds good. Let the final verdict in regard to the usefulness of quinidine in therapeutics be what it will, and the outlook is by no means unhopeful, the new knowledge gained from its reactions, the new lines of research

which they have suggested and will continue to suggest, are far from negligible. Quinidine is not only testing new current theories, but it is bringing valuable confirmation of older conclusions. One of the most striking of these is its final proof that fibrillation and flutter are fundamentally similar. Another incidental service which it is accomplishing, is that it is confirming the analysis of those cases of fibrillation in which the ventricle beats slowly. These cases have been interpreted as instances of combined fibrillation and heart-block; quinidine clearly displays this block when it restores the normal rhythm (Fig. 6). Recently we have treated a case of fibrillation in which the ventricle beat constantly and slowly at 30 to 40 per minute; when the auricle resumed its natural beat, complete block was disclosed. Quinidine will continue to bring knowledge of this kind; it is opening up many lines of original research.

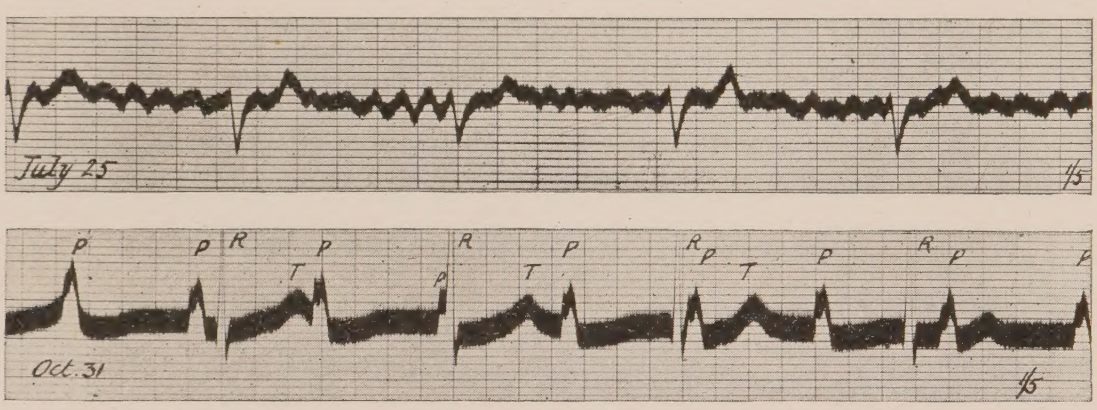


FIG. 6.—The upper is a curve taken on July 25 by leads from the chest wall. It shows fibrillation of the auricles and a slow and regular action of the ventricle. A single dose (0.6 of a gram) of hydroquinidine was given on October 31 and this restored the natural action of the auricle (lower curve). The mechanism is now one of complete heart-block; this continued unaltered.

If the theory of circus movement is finally accepted, careful research upon quinidine will continue to throw light upon the precise factors involved in the maintenance of this movement; it has yet to guide us further in arriving at a clearer idea of the real distinction between the two closely allied conditions, fibrillation and flutter.

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